

Prevalence of sinusitis and efficacy of intranasal corticosteroid treatment on asthmatic symptoms in asthmatic patients with rhinosinusitis: a pilot study

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Background: Prevalence of sinusitis on sinus computed tomography (CT) in asthmatic patients and efficacy of intranasal corticosteroid treatment on asthmatic symptoms in asthmatic patients with rhinosinusitis on sinus CT is unclear.

Methods: Sinus CT of asthmatic patients were evaluated using the Lund-Mackay system (LMS). Intranasal corticosteroid treatment (mometasone furoate) was newly added to symptomatic asthmatic patients with rhinosinusitis treated without intranasal corticosteroids, and the findings of the Asthma Control Test (ACT), Asthma Control Questionnaire in 5 items (ACQ5), spirometry, and sinus CT were evaluated before and 3 months after additional intranasal corticosteroid treatment.

Results: In a total of 160 asthmatic patients, rhinosinusitis and maxillary, ethmoidal, sphenoidal, and frontal sinusitis were observed in 75.0%, 70.0%, 53.1%, 33.1%, and 28.8%, respectively. Nasal symptoms and rhinophonia were observed in 81.9% and 72.5%, respectively, and patients with nasal symptoms and those with rhinophonia both showed significantly higher LMS scores in each sinus. Chronic rhinosinusitis (CRS) was observed in 66.9%, and these

patients had significantly more severe asthma than the patients without CRS. In patients with CRS, patients with rhinophonia showed significantly higher LMS scores than those without rhinophonia. ACT, ACQ5, and the value of the forced expiratory volume in 1 second (FEV₁) all significantly improved 3 months after the additive intranasal corticosteroid treatment in 24 patients, despite the fact that their LMS scores remained unchanged.

Conclusion: Additive intranasal corticosteroid treatment may be an effective treatment option for symptomatic asthmatic patients with rhinosinusitis. © 2015 ARS-AAOA, LLC.

Key Words:

rhinosinusitis; intranasal corticosteroid; asthma; sinus; computed tomography

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The association between bronchial asthma and rhinitis/rhinosinusitis is commonly observed, and clinical interest of the relationship between the upper and lower airways is increasing. Asthmatic patients have a greater prevalence of rhinosinusitis compared to those without asthma,¹

and chronic sinusitis was reported to be consistently associated with increased adjusted hospitalization rate induced by asthma exacerbations in patients ≥ 65 years old.² Patients with allergic rhinitis with or without bronchial asthma both showed airway hyperresponsiveness to methacholine³; an allergen challenge to the upper airway induced lower airway eosinophil infiltration, and airway hyperresponsiveness was also reported.⁴ Meanwhile, an allergen challenge to the lower airway can induce upper airway eosinophilic inflammation,⁵ bronchial hyperresponsiveness accompanying systemic eosinophilia may be directly related to atopic asthma, and the concepts of a united allergic airway and the united reaction of upper and lower airway inflammation have been proposed.^{6,7}

A strong association of asthma with chronic rhinosinusitis (CRS) has been reported,^{2,8,9} and a high prevalence

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of allergic rhinitis before diagnosing CRS has also been reported.¹⁰ Up to 80% of asthmatic patients have radiological sinusitis¹¹ and 88% of mild-to-moderate asthmatic patients demonstrated abnormal sinus computed tomography (CT) findings.¹²

Oka et al.¹³ showed that additive intranasal corticosteroid treatment (ICT) improved both asthmatic symptoms and the fraction of exhaled nitric oxide (FENO) in asthmatic patients with allergic rhinitis. However, the efficacy of ICT for asthmatic symptoms among asthmatic patients with CT-diagnosed rhinosinusitis has not yet been clarified. We postulated that ICT might be beneficial for asthma symptoms in asthmatic patients with CT-diagnosed rhinosinusitis, and evaluated the efficacy of additive ICT in addition to the prevalence of sinus CT findings in asthmatic patients.

Patients and methods

Patients

This study was performed at the University of Occupational and Environmental Health, Japan (UOEH) and related hospitals in Japan between April 2010 and December 2013. Asthmatic patients who fully satisfied the standard criteria for asthma, according to the Global Initiative for Asthma,¹⁴ were eligible. The inclusion criteria were as follows: (1) age over 20 years; (2) the ability to perform an adequate spirometric maneuver; (3) receiving anti-asthmatic agents including inhaled corticosteroids for at least 8 weeks; and (4) a nonsmoking status during the study. The exclusion criteria were as follows: (1) having a history of any upper and lower respiratory tract infections within at least 1 month before the present study; (2) having uncontrollable chronic respiratory infections; (3) having chronic obstructive pulmonary disease; (4) being pregnant; and (5) having an asthma exacerbation during the 8 weeks before the study.

Study design

This was a multicenter, observational, cross-sectional survey and uncontrolled longitudinal open-label study. This study was approved by the Ethics Committee of UOEH, and it was conducted in accordance with the principles of the Declaration of Helsinki. Informed consent was obtained prior to the study. The treatment steps of asthmatic patients were evaluated by the Japanese guidelines for adult asthma.¹⁵ Sinus CT was evaluated according to the Lund-Mackay scoring system (LMS).¹⁶ Patients with an LMS score of >1 without ICT were recruited, and the Asthma Control Test (ACT) and Asthma Control Questionnaire 5-item version (ACQ5) were evaluated. Patients with rhinosinusitis and ACT score <25 and/or ACQ5 score >0 were enrolled into the group assigned to receive additive ICT when the patient agreed to participate in the study. ICT (100 µg of nasal mometasone furoate treatment to each nasal cavity daily) was newly administered for 3 months

with continuing all other anti-asthmatic medications with no changes and no additional treatments including antimicrobials during the study. Each patient completed the questionnaires of ACT, ACQ5, and the spirometry before and 3 months after the start of additive ICT. Serum total immunoglobulin E (IgE) (radioimmunosorbent test [RIST]) and peripheral blood eosinophil count before adding ICT were also evaluated.

The definition from the European Position Paper on Rhinosinusitis and Nasal Polyps 2007 (EPOS 2007) for chronic rhinosinusitis was used for the diagnosis of CRS in this study.¹⁷

Radiological measurement of sinus CT

Sinus CT was performed in a supine position, and 3-mm axial and coronal images were collected. The findings were reviewed by 2 investigators (KY and SN) who were blinded to the clinical information, and the average values were analyzed, using LMS¹⁶ and the olfactory cleft (OC) score.¹⁸

Evaluation of nasal symptoms and rhinophonia

Nasal symptoms were assessed according to EPOS 2007,¹⁷ and patients with at least 1 of the nasal symptoms that were described in that article were considered as positive for nasal symptoms. Rhinophonia, mainly rhinolalia clausa, was evaluated according to auditory impressions by the attending physicians.

Subjective asthmatic symptom measurement

ACT

The ACT consists of 5 questions assessing asthma control,^{19,20} and the Japanese version of the ACT was adequately validated in Japanese asthmatic patients.²¹ A score of 20 or higher was identified as well-controlled, and a difference of 3 points was considered to be the minimally important difference (MID).²²

ACQ5

The ACQ5 (Japanese version) consists of 5 items, and is expressed as the mean of the 5 scores.²² A value of ≤0.75 and ≥1.50 is considered to indicate well-controlled and not well-controlled asthma, respectively.²³ A difference of 0.5 points or more was considered to be the MID.²⁴

Pulmonary function test

Spirometry (FUDAC-77; Fukuda Denshi, Tokyo, Japan) was performed at the start of the additive ICT and then again 3 months after the additional ICT, between 9:00 AM and 11:30 AM. The use of additive short-acting β₂ agonists was prohibited for at least 6 hours prior to the spirometry evaluation, but regular treatment of inhaled corticosteroid/long-acting beta-agonist (ICS/LABA) was used around 7:00 AM as usual. The vital capacity (VC), forced vital capacity (FVC), forced expiratory volume in 1 second (FEV₁), and peak expiratory flow (PEF) were

TABLE 1. Clinical characteristics of the patients

		Female/Male (n)
Patients, n	160	84/76
Age (years), mean (range)	62.6 (25–91)	
Nasal symptoms, n (%)	131 (81.9)	70/61
Rhinophonia, n (%)	116 (72.5)	61/55
Chronic rhinosinusitis, n (%)	107 (66.9)	54/53
With nasal polyp	21 (19.6)	12/9
Without nasal polyp	86 (80.4)	42/44
ICS, n (%)		
ICS	30 (18.8)	
ICS/LABA	130 (81.2)	
Treatment steps, n (%) ^a		
1	1 (0.6)	
2	27 (16.9)	
3	85 (53.1)	
4	47 (29.4)	

^aTreatment steps were used according to the Japanese guidelines of adult asthma.¹⁵

ICS = inhaled corticosteroid, LABA = long-acting beta-agonist.

measured according to the formula of the Japanese Respiratory Society.²⁵

Statistical analyses

All values are expressed as means with ranges or standard deviation. Continuous variables were compared using the Mann-Whitney *U* test and Student *t* tests, whereas categorical variables were compared using Fisher's exact test or the chi square test, as appropriate. The SPSS software package (version 19; IBM Corp., Armonk, NY) was used, and a $p < 0.05$ was considered significant.

Results

Patient characteristics

The patient characteristics of enrolled 160 (84 females; 76 males) Japanese asthmatic patients are shown in Table 1. All patients received ICS or ICS/LABA treatment. Nasal symptoms and rhinophonia were frequently observed in 81.9% and 72.5%, respectively, and CRS was categorized in 66.9%.

Asthma treatment steps in patients with nasal symptoms and rhinophonia are shown in Figure 1. Asthmatic patients with nasal symptoms and patients with rhinophonia both included significantly more step 4 patients ($p < 0.05$) (Fig. 1A, B). The patients with nasal symptoms tended to be more frequently included in treatment steps 3 or 4 ($p < 0.05$) (Fig. 1A).

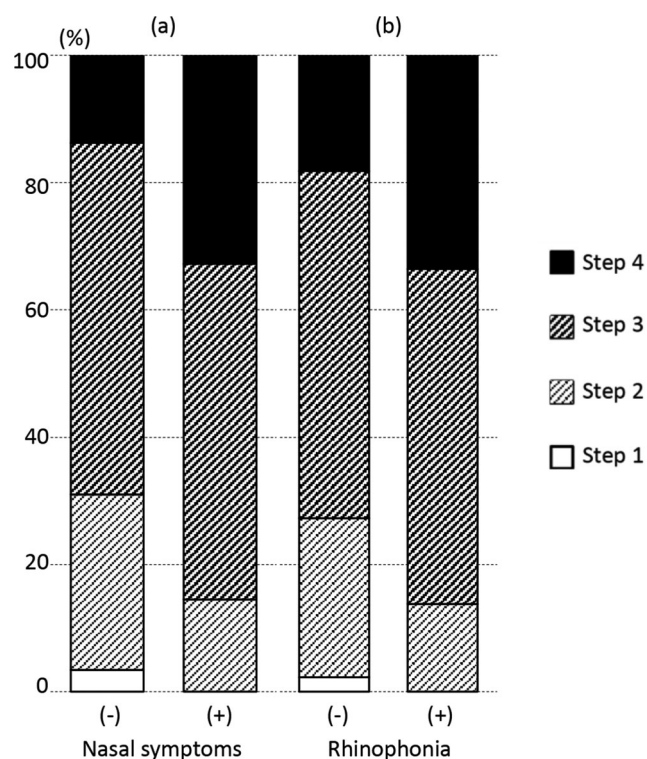


FIGURE 1. The treatment steps in patients with or without nasal symptoms or rhinophonia. The differences in the treatment steps in asthmatic patients with nasal symptoms (A) and rhinophonia (B). (A) More severe patients with treatment step 4 ($p < 0.05$) and step 3 or 4 ($p < 0.05$) were significantly observed in asthmatic patients with nasal symptoms. Asthmatic patients with nasal symptoms included (treatment step 4) ($p < 0.05$). (B) In addition, asthmatic patients with rhinophonia demonstrated significantly more severe patients (treatment step 4) ($p < 0.05$).

Radiological features of sinus CT

The results of the LMS scores are shown in Figure 2A, and equal to the relationship between the LMS scores and the treatment steps are shown in Figure 2B. Rhinosinusitis with more than and equal to 1 LMS score was observed in 75.0%. Maxillary (70.0%) sinusitis was most frequently observed, followed by ethmoidal (53.1%), sphenoidal (33.1%), and frontal (28.8%) sinusitis. Nasal polyps and postoperative changes were observed in 15.6% and 8.1%, respectively. Total LMS scores tended to increase with asthma severity (Fig. 2B).

The LMS scores in patients with nasal symptoms and rhinophonia are shown in Figure 2C and D. Patients with nasal symptoms showed significantly higher total LMS scores and scores in all sinus lesions including the ostiomeatal complex (OMC) and OC than patients without nasal symptoms (Fig. 2C). Similar results were observed in asthmatic patients with rhinophonia compared to those without rhinophonia (Fig. 2D).

Asthmatic patients with CRS

Nearly 67% of patients were categorized as having CRS (66.9%), including 8 patients with CRS with nasal polyps (CRSwNP) (Table 1). Patients with treatment step 4 and those with steps 3 or 4 were both significantly higher

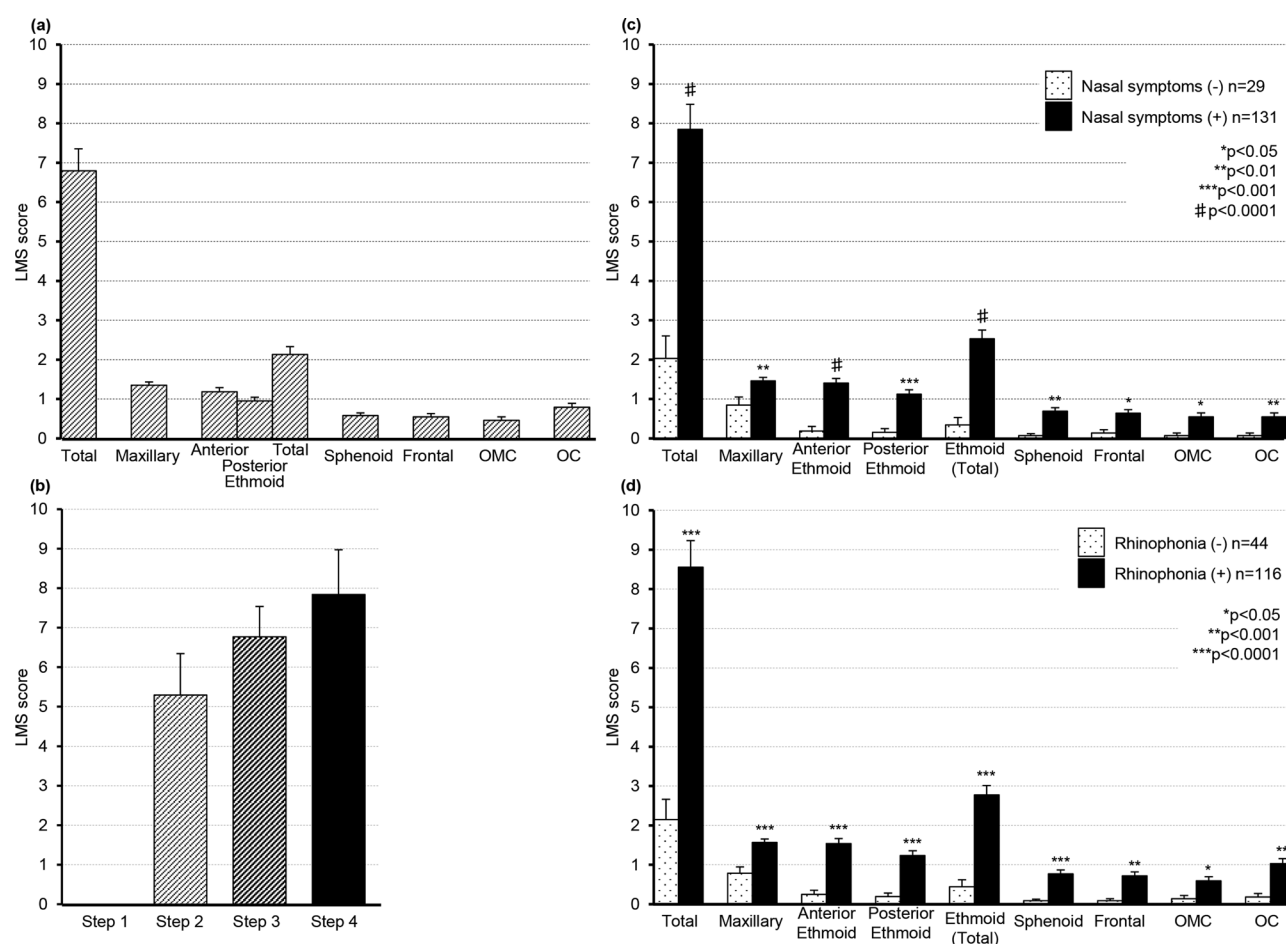


FIGURE 2. The LMS scores in patients with asthma. (a) The LMS scores in each sinus in all patients. (b) LMS scores in a different treatment steps. LMS scores in each sinus in asthmatic patients with or without nasal symptoms (c) and rhinophonia (d). LMS = Lund-Mackay system; OC = olfactory cleft; OMC = ostiomeatal complex.

($p < 0.01$ and $p < 0.05$, respectively) in CRS patients than in patients without CRS (Fig. 3A). There were no differences between the LMS scores in patients with CRSwNP and those with CRS without nasal polyps (CRSsNP) (Fig. 3B). In patients with CRS, CRS patients with rhinophonia showed significantly higher total LMS scores and scores in anterior, posterior ethmoid, and frontal sinuses than CRS patients without rhinophonia (Fig. 3C).

Effect of additive intranasal corticosteroid treatment on asthmatic symptoms

Table 2 represents the characteristics of the patients treated with additive ICT. Medication adherence during the study was confirmed by the doctors, pharmacists and nurses, and no major problems were seen among the subjects included in the additive ICT study.

Subjective asthmatic symptom measurements ACT

The ACT scores improved significantly from 20.3 ± 4.1 to 22.9 ± 2.5 ($p < 0.001$) after the additive ICT, including 11

TABLE 2. Patient characteristics with respect to the additive intranasal treatment

n (F/M)	24 (11/13)
Age (years), mean (range)	66.0 (26–83)
Duration of asthma (years), mean	16.0
ICS, n	
MF-DPI	7
BUD/FM-DPI	15
CIC-HFA-MDI	1
BUD/FM-DPI + MF-DPI	1
Treatment steps, n (%) ^a	
3	10 (41.7)
4	14 (58.3)

^aTreatment steps were used according to the Japanese guidelines of adult asthma.¹⁵

BUD/FM-DPI = budesonide/formoterol-dry powder inhaler; CIC-HFA-MDI = ciclesonide-hydrofluoroalkane-metered dose inhaler; ICS = inhaled corticosteroid; MF-DPI = mometasone furoate-dry powder inhaler.

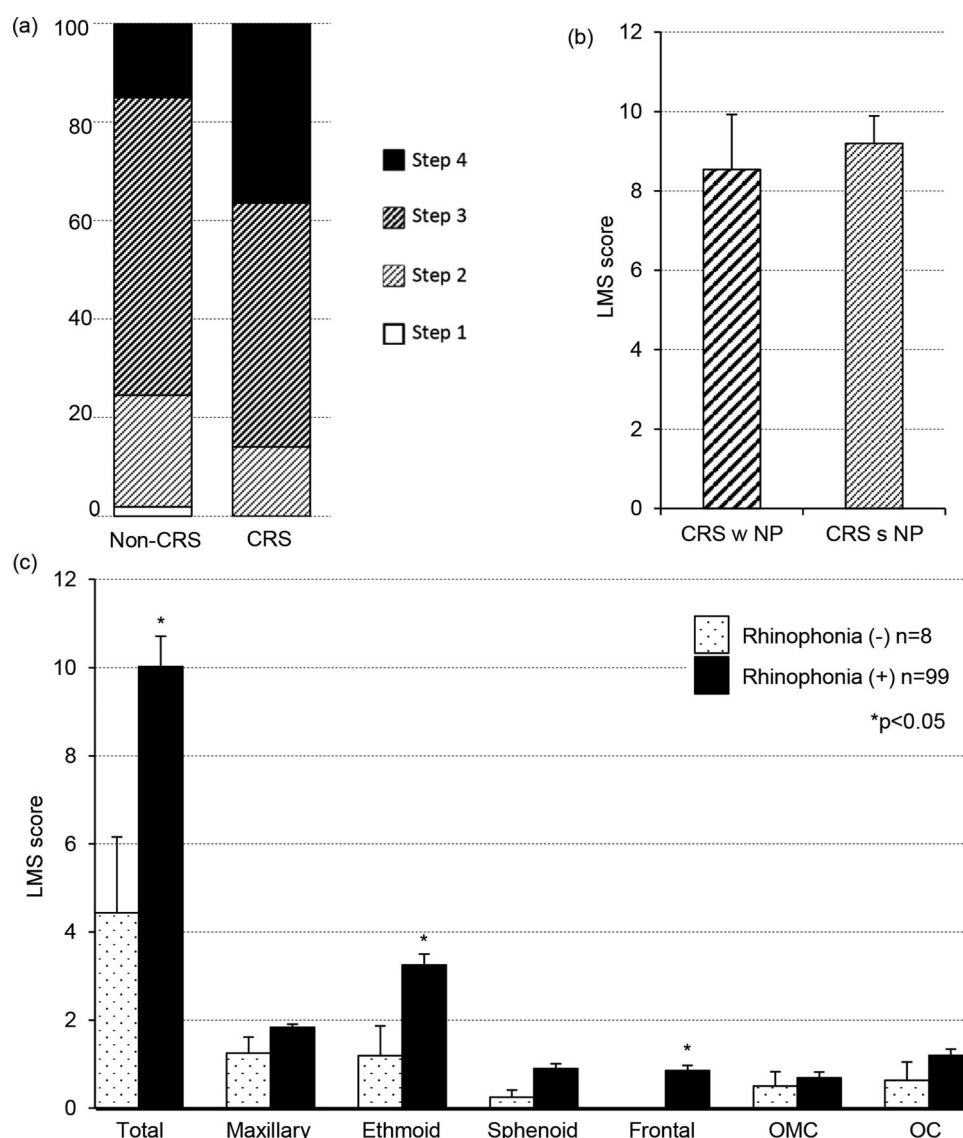


FIGURE 3. The treatment steps and LMS scores in asthmatic patients with CRS. (A) Asthmatic patients with CRS represented more severe patients (treatment step 4) compared to the patients with non-CRS. (B) There were no significant differences between the asthmatic patients with CRSwNP and those with CRSsNP. (C) The LMS scores of each sinus in the asthmatic patients with or without CRS. The total scores, scores of ethmoid and frontal sinuses were significantly higher in the asthmatic patients with CRS compared to the patients without CRS. CRS = chronic rhinosinusitis; CRSsNP = CRS without nasal polyps; CRSwNP = CRS with nasal polyps; LMS = Lund-Mackay system; OC = olfactory cleft; OMC = ostiomeatal complex.

patients (45.8%) who showed an improvement satisfying MID (Fig. 4A). The patients with ACT scores ≥ 20 (good control) significantly increased from 58.3% to 95.8% ($p < 0.005$), and patients who achieved ACT scores of 25 (total control) increased from 12.5% to 29.2% after the additive ICT.

ACQ5

The average ACQ5 scores significantly improved from 1.86 ± 1.2 to 1.02 ± 0.8 ($p < 0.01$) after additive ICT (Fig. 4B), and 13 patients (54.2%) showed an improvement satisfying MID 3 months after the additive ICT. ACQ5 scores of ≤ 0.75 (well-controlled) were noted from 16.7% to 37.5% after the additive ICT; conversely, the number of patients

with ACQ5 scores of > 1.5 (uncontrolled) significantly decreased from 54.2% to 20.8% ($p < 0.05$).

Pulmonary function test

The values of VC, FEV₁, and PEF tended to increase 3 months after the additive ICT, and the value of FEV₁ only showed a significant improvement after the additive ICT (Fig. 5).

Changes in the sinus CT scores

The total LMS scores and the scores of the ethmoid sinuses tended to decrease after the additive ICT, but these changes were not statistically significant (Fig. 6).

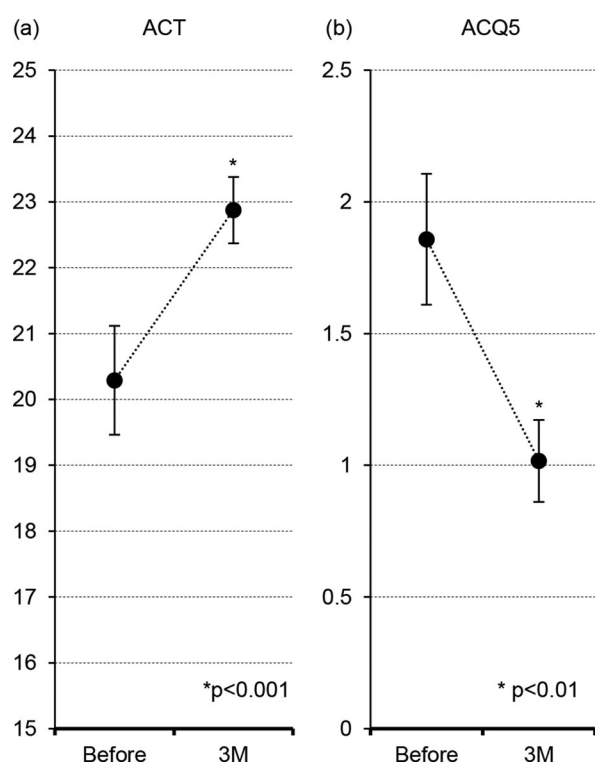


FIGURE 4. The changes of ACT and ACQ5 before and after the additive intranasal corticosteroid treatment. The scores of the ACT (A) and the ACQ5 significantly improved 3 months after the additive intranasal corticosteroid treatment. 3M = 3 months; ACQ5 = Asthma Control Questionnaire in 5 items version; ACT = Asthma Control Test.

Serum IgE-RIST and peripheral blood eosinophil count

Average values of serum IgE-RIST and peripheral blood eosinophil counts were 686.6 ± 663.2 IU/L and $521.0 \pm 688.5/\mu\text{L}$, respectively. These values were not statistically related to an improvement of ACT and ACQ5 fulfilling MID and each spirometric parameter.

Discussion

Herein, we showed the radiologic features of rhinosinusitis among patients with asthma; this is the first report of the possible efficacy of additive ICT on asthmatic control and spirometric data in symptomatic asthmatic patients with CT-diagnosed rhinosinusitis. In addition to subjective asthmatic symptom improvement satisfying the criteria for MID of the ACT and ACQ5 in about one-half of the patients (Fig. 4), a significant improvement of FEV₁ at 3 months after the additive ICT was shown in patients with incompletely controlled asthma complicating rhinosinusitis (Fig. 5), even without significant improvement of LMS scores (Fig. 6).

Our results showing that the radiological severity of rhinosinusitis tended to increase with asthma severity (Figs. 1 and 2) are consistent with previous observations.^{26–28} A similar trend has also been reported in CRS,⁹ and a decreased lung function was also observed

in CRS patients, but the LMS scores were not related to the lung function.²⁹ Nasal symptoms and rhinophonia are important predictors of the radiological findings of rhinosinusitis, and ethmoid involvement was closely related to the diagnosis of CRS compared to maxillary sinus findings (Fig. 3C).

Proposed possible mechanisms to explain the interaction between the upper and lower airways include nocturnal aspiration of sinus secretions into the lungs, enhanced vagal stimulation, mouth breathing–induced excessive drying of the lower respiratory tract, the production of bacterial toxins in the sinus that may induce partial beta blockade, the production of cytokines and bronchoconstrictive mediators in the sinus,³⁰ and postnasal drip–induced pharyngeal mucosal damage.^{31,32} The provocation of allergen on both the nose and bronchi can induce both nasal and bronchial symptoms in addition to a reduction of pulmonary and nasal function.^{4,5} Inflammation of the sinus tissue not only releases inflammatory mediators into the circulation involving bone marrow stimulation, but it also releases chemotactic factors that recruit inflammatory cells, such as eosinophils from the bone marrow to the circulation, which then immigrate into both the upper and lower airways.^{4–6,33–36}

Bronchial asthma including aspirin-induced asthma is well known to be a comorbid disorder of recently proposed eosinophilic chronic rhinosinusitis (ECRS),^{37,38} especially in nonallergic subjects.^{39–41} ECRS is characterized by ethmoid sinus–dominant eosinophil infiltration, frequently associated with moderate to severe asthma, especially in most patients with aspirin-intolerant asthma complicated with CRS. Patients with ECRS may be included in part in this study, even though no clear definition and diagnostic criteria of ECRS have yet been established. Upper airway inflammation can cause lower airway hyperresponsiveness in a mouse model of rhinosinusitis and asthma,⁴² suggesting that a close relationship may exist between ECRS and asthma or some other predisposing asthmatic conditions. The most dramatic difference in the findings of sinus CT in patients with ECRS compared with those without ECRS was the involvement of the posterior ethmoid sinusitis and the olfactory cleft, especially in the early stage of patients with ECRS; the maxillary sinus was not different.⁴³ Ethmoid sinus involvement was frequently observed, especially in asthmatic patients with CRS (Fig. 3C) and rhinophonia (Fig. 2D) compared to those with maxillary sinus involvement in this study. Possible interracial or interethnic differences of CRS have been reported,⁴⁴ and careful consideration might be necessary to interrupt our results with the Japanese population.

Recommended treatments for both CRS with or without nasal polyps are topical corticosteroids,⁴⁵ and ICT has been reported to improve both the asthmatic symptoms and quality of life of patients with mild intermittent asthma.^{46,47} In addition, topical corticosteroids as well as systemic corticosteroids are keys for treating patients with ECRS,⁴⁸ and ICT may be a good treatment

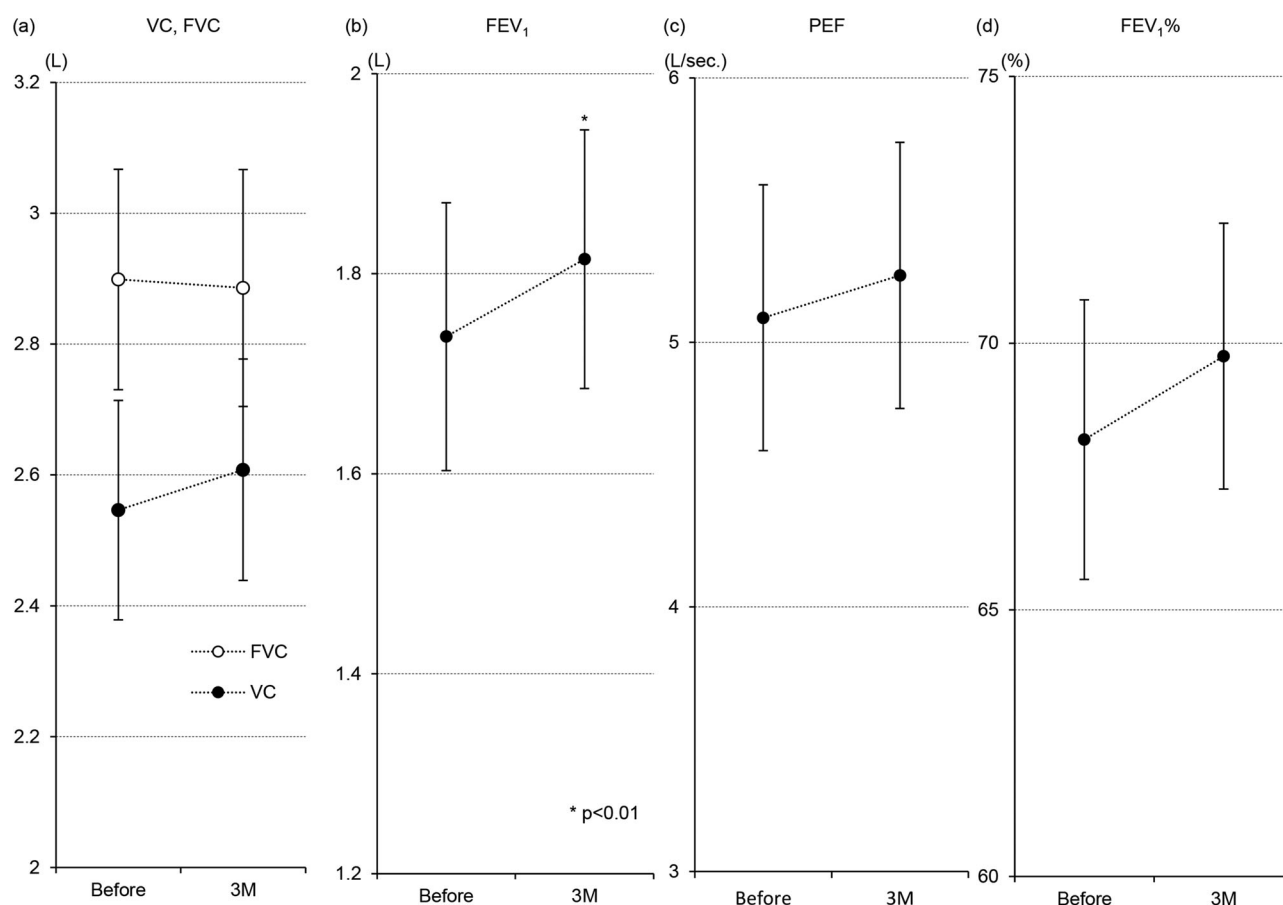


FIGURE 5. The changes in the VC, FVC, FEV₁, and PEF before and after additive intranasal corticosteroid treatment. The changes in the VC (closed circle) and FVC (open circle) (A), FEV₁ (B), PEF (C), and the FEV₁% (D) before and 3 months after the additive intranasal corticosteroid treatment. The plots show the averages and standard errors. The values of FEV₁ significantly improved at 3 months after the additive intranasal corticosteroid treatment ($p < 0.05$). 3M = 3 months; FEV₁ = forced expiratory volume in 1 second; FEV₁% = ratio of the FEV₁ to the FVC; FVC = forced vital capacity; L = liter; L/sec. = liter/second; PEF = peak expiratory flow; VC = vital capacity.

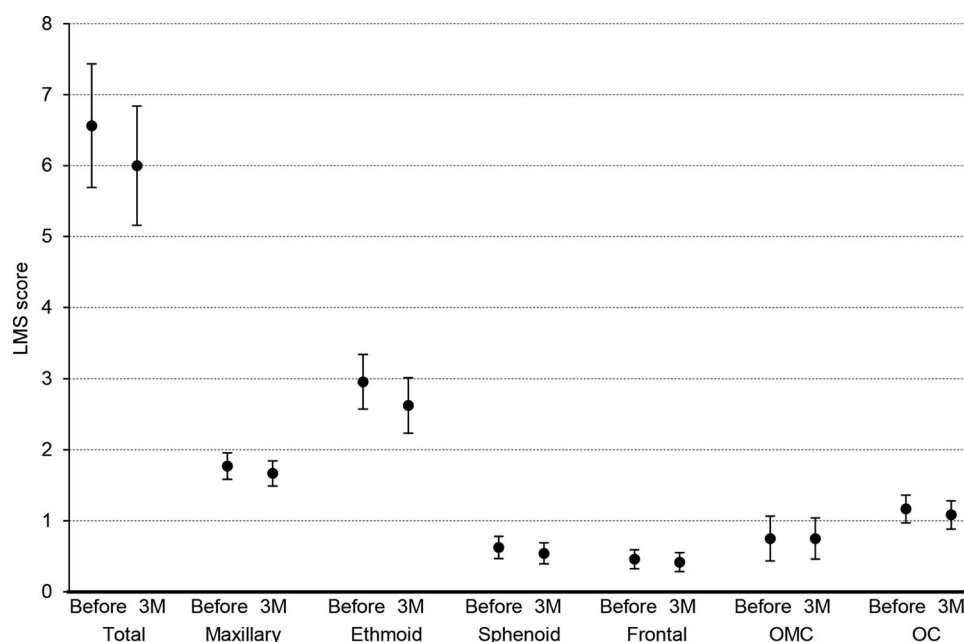


FIGURE 6. The changes in the LMS scores before and after the additive intranasal corticosteroid treatment. There were no significant changes in the LMS scores in each sinus before and 3 months after the additive intranasal corticosteroid treatment. 3M = 3 months; LMS = Lund-Mackay system; OC = olfactory cleft; OMC = ostiomeatal complex.

strategy in ECRS cases with asthma. Regarding the treatment of nasal polyposis that may be pathologically closely related to ECRS, several randomized, placebo-controlled trials have demonstrated the efficacy of various topical corticosteroids, including mometasone furoate used in this study,⁴⁹ and similar beneficial effects of additive ICT on the symptoms and control of asthma and rhinitis have been reported.^{34,35,46,47,50,51} ECRS can partially be treated with ICT; further studies are necessary to elucidate the clinical role of ICT on asthmatic conditions in asthmatic patients with rhinosinusitis.

Study limitations

There are several limitations associated with this study. First, this study was an uncontrolled, open-label, non-crossover study with only a small number of patients and a relatively short duration, without a control group and no randomization of subjects. However, the purpose was to evaluate the effects of additive ICT in a simple clinical

choice as a pilot study. Second, we only enrolled patients who were already treated for asthma and who still had asthmatic symptoms without any ICT. Third, some selection bias is possible because this study was performed among outpatients in a hospital-based clinical situation. Fourth, only Japanese patients were recruited, and ethnic differences have to be considered. Fifth, inflammatory markers such as fractional exhaled nitric oxide (FeNO), nasal nitric oxide (NO), and cellular examination were not evaluated. Further studies are necessary; however, we believe that our data nevertheless support the concept of an interaction between the upper and lower airways in asthmatic patients with rhinosinusitis.

Conclusion

Sinus CT is useful for evaluating the indirect impact of rhinosinusitis on asthmatic symptoms, and additive ICT may be an effective option to achieve better control of asthma in patients with rhinosinusitis. ☯

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